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EXAMINER
MITCHELL, GREGORY W

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/678,292	**Applicant(s)** KEPPLER, BERNHARD	
	Examiner Gregory W Mitchell	**Art Unit** 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2003*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-12* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☒ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending and are examined herein.

Priority

This application is a continuing application of PCT/EP02/03560, filed on March 28, 2002, which claims foreign priority to German Application 101 16 527.7, filed on April 3, 2001. Applicant's priority is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *treatment* of *specific cancers*, such as adenocarcinoma of the colon, teratocarcinoma of the testis, etc., utilizing a bis(2-acetylpyridine-4,4-dialkyl thiosemicarbazonato-N1,N2,S)gallium(III) tetrachlorogallate(III) such as the one illustrated on Example 1 on the bottom of page 6, does not reasonably provide enablement for (1) *prophylaxis* of (2) *a cancer illness in general*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Foreman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) *The Nature of the Invention*:

The invention is drawn to a method for the prophylaxis or treatment of a cancer illness, in general, by administering to a living organism an effective amount of a thiosemicarbazone/gallium complex.

(2) *Breadth of the Claims*:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. According to the Merriam-Webster Third New International Dictionary (1961, p. 1818, middle column), the term "prophylaxis" means "the prevention of disease." Therefore, the claimed invention includes the prevention any form of cancer; that is, it provides prevention in both those living organisms, including humans, known to be at risk for cancer as well as those that would not normally be expected to develop cancer. Accordingly, the term "prevention" indicates a claim whereby those normally not at risk for developing a cancer illness would be prevented from ever developing cancer with any of the numerous derivatives/complexes claimed herein.

(3) ***Guidance of the Specification***:

The guidance of the specification as "prophylaxis" of a cancer illness is completely lacking. The specification speaks only of "high tumour inhibiting activity." Inhibiting cancer is not identical to preventing cancer. Furthermore, Applicant claims the treatment of cancer in general but indicates that the thiosemicarbazone/gallium complex bis(2-acetylpyridine-4,4-dimethyl thiosemicarbazonato-N1,N2,S)gallium(III) tetrachlorogallate(III) in example 1 is only capable of "high tumor inhibiting activity." Not all cancerous illnesses comprise tumorous growth, nor is high inhibiting activity equivalent to prevention. Finally, the specification does not provide any evidence indicating that each of the various thiosemicarbazone/gallium complexes would have identical results to the previously mentioned dimethyl derivative of Example 1.

(4) ***Working Examples***:

Applicant does not provide any working examples of the treatment of a living organism utilizing any of the gallium complexes of the claimed invention. Applicant provides minimal (i.e. IC_{50} values) that resulted from in-vitro testing of a single gallium complex on three types of carcinoma cell lines. Applicant also provides subjective evidence that the gallium complexes claimed therein have "comparable effects" on two other forms of cancer.

(5) ***State of the Art***:

The state of the art regarding the *treatment* of *specific cancers* is high. The state of the art regarding the *prevention* of *cancers in general* is extremely underdeveloped. The state of the art regarding the use of thiosemicarbazones is somewhat developed.

Please note that there is no known anticancer agent which is effective against all cancers. Carter, et al. (*Chemotherapy of Cancer*, 2nd ed.) clearly teaches that for the forty known anticancer agents, none are effective against all cancers (pages 362-365). There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect a single organ are often not generally treatable. For example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Finally, reasonable guidance with respect to *preventing* any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

(6) *Predictability of the Art*:

The invention is directed to *prophylaxis* or treatment of cancer illnesses in *general* with gallium complexes comprising a *generally described structure*. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter et al. and the state of the art in (5) that shows the different treatments of cancers and Hall et al. regarding the state of thiosemicarbazones as anti-cancer agents. The treatment of one type of cancer could not be necessarily the same for the other type.

Also note that one of ordinary skill in the art would recognize that it is highly unpredictable in regard to what population will develop cancer, as discussed at the end of (5) above. In order to administer the agent to the population at large, one would need to consider the therapeutic effects, side effects and especially serious toxicity that may be generated by drug-drug interactions when and/or after administration to a living organism (e.g., a human) a gallium complex of the instant invention.

As noted above, different thiosemicarbazone compounds have been shown to have significantly different results in their treatment of cancer. Accordingly, the effectiveness of any given compound of the instant invention would need to be determined individually. If one thiosemicarbazone is capable of having an effectiveness 1/3 that of another, is it not conceivable that another would have an effectiveness 1/3 the first? Or no effectiveness at all? Furthermore, the LD_{50} values of the gallium complex are unpredictable as they are not disclosed by Applicant. Accordingly, the toxicity of the compounds is undisclosed and unpredictable, as well.

(7) *The Quantity of Experimentation Necessary*:

In order to practice the disclosed invention, one would need to test the combination in the model system to determine effectiveness of the compound at treating a given cancer *in vitro*. If unsuccessful, which is likely given the fact that the treatment of all cancers with a single agent is unknown, one of skill in the art would have to then either envision a modification of the thiosemicarbazone of the gallium complex and test the system again. Alternatively, one would have to decide upon a new type of cancer to test the agent against and test the system again. Following either success or failure of any given test, the entire, unpredictable process would have to be repeated until an understanding of which types of cancer illnesses were treatable with the agent was determined.

As discussed above, the specification fails to provide sufficient support for determining all living organisms susceptible to cancer in order to allow one of ordinary skill in the art to be capable of administering to a population the gallium complexes of the instant invention for the _prevention_ *of cancer in general*. As a result, one of skill in the art would be forced to perform an exhaustive search for the population of living organisms that will develop cancer and, thereby, use the instant invention.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and '[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly, the claims are evaluated as being a method of treatment; the method of prophylaxis is not considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collery et al. (WO 93/02087) in view of Hall et al. (*Anti-Cancer Drugs*, 4, p. 231).

Collery et al. teaches that gallium(III) complexes exhibit anti-tumor activity (p. 1, lines 1-5). Collery et al. further teaches that gallium(III), when complexed to N-heterocycles, shows antitumor activity (p. 1, line 34-p. 2, line 2; and bottom of p. 26-top of p. 27). Furthermore, it is taught that when possessing a positive charge, the counter-ion of these anti-cancerous gallium(III) complexes is either Cl^- or $[GaCl_4]^-$ (p. 2, lines 3-35).

Collery et al. does not specifically teach the use of a gallium(III) complex wherein the N-hetercyclic ligand is a thiocarbazone nor does it specifically teach the treatment of humans.

Hall et al. teaches that thiosemicarbazone when complexed to nickel, copper and cobalt are effective at inhibiting carcinoma *in vivo* (p. 232). Hall et al. also teaches that thiosemicarbazones, themselves, are effective at treating carcinoma and that the metal complexes did not appear to be a necessary requirement for the thiosemicarbazone cytotoxicity but that slightly different metals and/or chemical moieties could slightly affect the magnitude of inhibition (pp. 232 and 239). Hall et al. specifically teaches an anti-neoplastic agent wherein a pair of 2-acetylpyridine-4,4-diethyl thiosemicarbazone molecules are complexed to nickel (compound 4, p. 232). Hall et al. also teaches that the thiosemicarbazone-metal complexes are effective at inhibiting cancerous growth of human tissue (p. 234, Table 2).

It would have been obvious to one of ordinary skill in the art to replace the N-heterocycle of the gallium(III) complex of Collery et al. with a thiosemicarbazone of Hall et al. because 1) the thiosemicarbazones of Hall et al. *are* N-heterocycles; and 2) both gallium(III) complexes and thiosemicarbazones are each independently known to be effective anti-cancer agents, as taught by Collery et al. and Hall et al., respectively. Furthermore, it would have been obvious to treat humans with such a complex because, as taught by Hall et al., thiosemicarbazone-metal complexes were effective at inhibiting cancerous growth of human tissue (p. 234, Table 2).

One would have been motivated to replace N-heterocycles of Collery et al. with the thiosemicarbazone of Hall et al. because 1) of an expectation of success in preparing a complex with similar anti-cancerous activity in human cells to those found for various other such metal complexes of both the gallium(III) complexes of Collery et al. and of the thiosemicarbazone-metal complexes of Hall et al. and 2) because Hall et al. teaches that by switching the metal portion of the complexes taught therein, a different magnitude of cancer inhibition can be achieved. One would have had an expectation of success because N-heterocyclic-gallium(III) complexes and thiosemicarbazones are both independently known to possess anti-cancerous activity in human cells, as taught by both Collery et al. and Hall et al., and it would be expected that a combination thereof would provide similar results. Furthermore, one would have expected such a combination to provide similar results because Hall et al. had already shown that thiosemicarbazones and thiosemicarbazone-metal complexes possesses similar anti-cancerous activities and had suggested switching the metal portion of the metal complex to provide different magnitudes of cancer inhibition (p. 232, Table 1; p. 236, Table 2; and p. 239).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8 AM - 4 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm

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